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Pharmacokinetics and Bioavailability of Zidovudine and Its Glucuronidated Metabolite in Patients with Human Immunodeficiency Virus Infection and Hepatic Disease (AIDS Clinical Trials Group Protocol 062)

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The pharmacokinetics of zidovudine (ZDV) are established in patients with various stages of human immunodeficiency virus (HIV) disease. This study was conducted to determine the pharmacokinetic parameters of ZDV in patients with asymptomatic HIV infection and liver disease. HIV-infected volunteers with normal renal function were stratified according to the severity of liver disease (seven of eight were classified as mild). Each subject received a single intravenous dose of ZDV (120 mg) on the first day, followed by a single oral dose of ZDV (200 mg) on the second day. Blood samples were obtained over an 8-h collection interval, and concentrations of ZDV and its glucuronidated metabolite (GZDV) were determined by high-performance liquid chromatography. The following pharmacokinetic parameters were obtained after oral administration of ZDV to HIV-infected patients with mild hepatic disease; these values were compared with previously reported data in healthy volunteers. The area under the curve (AUC) (1,670 ± 192 ng · h/ml), maximum concentration of drug in serum (1,751 ± 180 ng/ml), and half-life (2.04 ± 0.38 h) of ZDV were increased, while the apparent oral clearance (1.57 ± 0.31 liter/h/kg of body weight) was decreased; AUC (7,685 ± 1,222 ng · h/ml) and maximum concentration of drug in serum (5,220 ± 1,350 ng/ml) of GZDV and the AUC ratio of GZDV to ZDV (2.79 ± 0.43) after oral administration were decreased. ZDV absolute bioavailability was 0.75 ± 0.15 in HIV-infected patients with mild hepatic disease. Although the ZDV apparent oral clearance was not impaired as significantly as in patients with biopsy-proven cirrhosis, our results suggest that ZDV could accumulate in HIV-infected patients with mild hepatic disease because of impaired formation of GZDV. Patients with mild hepatic disease may require dosage adjustment to avoid accumulation of ZDV after extended therapy.

Zidovudine (ZDV) has demonstrated clinical efficacy with decreased morbidity and mortality in patients with asymptomatic or more severe human immunodeficiency virus (HIV) disease (4, 7). Although data support the use of ZDV in selected patients, the drug is associated with significant toxicity in advanced HIV disease which is most commonly manifested by suppression of the circulating erythrocyte and neutrophil counts (18). Individual patients exhibit substantial variability in their ability to tolerate chronic ZDV treatment.

The pharmacokinetic disposition of ZDV in HIV-infected patients without evidence of hepatic disease has been described previously (1, 3, 12). ZDV was rapidly absorbed; the time to reach peak concentrations in plasma ranged from 0.6 to 0.8 h. The average oral bioavailability was about 65%, with 17 to 23% of an intravenous (i.v.) dose excreted unchanged in the urine. The volume of distribution at steady state was approximately 1.4 liters/kg of body weight, the average total body clearance (CL) was 1.3 to 1.6 liters/h/kg, and the elimination half-life ($t_{1/2}$) of ZDV was approximately 1 h. Approximately 60% of an i.v. dose was recovered as 3′-azido-3′-deoxy-5′ glucuronylthymidine (GZDV) in urine. After oral dosing, about 14% and 75% of the dose were recovered in urine as ZDV and GZDV, respectively.

ZDV is eliminated primarily by hepatic conjugation to an inactive glucuronyl derivative, GZDV. Glucuronidation activity has been thought to be preserved in various types of liver disease (20). However, current evidence suggests that glucuronidation of some substances may be impaired in hepatic dysfunction. For example, the hepatic extraction of morphine, a drug that is rapidly cleared and extensively glucuronidated, was reduced 25% in eight male patients with biopsy-proven ethanol-induced cirrhosis compared with controls (5). Additional observations suggested that the reduction in morphine's hepatic extraction ratio was a consequence of impaired hepatic enzyme capacity as opposed to decreased liver blood flow.

The disposition of ZDV is similar to morphine. ZDV is not extensively protein bound (<25%), and the CL of ZDV in humans is approximately 1,900 ml/min/70 kg of body weight, similar to hepatic blood flow (1). The oral clearance (CL/F, where F is absolute bioavailability) of ZDV and the formation clearance of GZDV were decreased in HIV-seronegative patients with biopsy-proven liver cirrhosis compared with HIV-seronegative controls (22). Decreased elimination of ZDV because of liver dysfunction may be particularly common among HIV-infected hemophiliacs and i.v. drug users who have a high frequency of chronic hepatitis due to infection with other blood-borne viruses. Patients with opportunistic infections

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TABLE 1. Patient laboratory values and demographics[a]

Patient	Site	Group[b]	Wt (kg)	Age (yr)	Gender	ALT (IU)	TB (mg/dl)	PT (s)	Alb (g/dl)	Serology and other characteristics	Clinical sign(s)
1	UNC	A	69.7	45	M	58	0.5	12.0	3.9	Anti-HBsAg, anti-HBc, chronic active hepatitis, hemophilia A	None
2	UM	A	59	26	F	74	0.6	12.4	4.0	Hepatitis nonA, nonB	None
3	UM	A	81.4	31	M	131	0.6	11.8	4.5	HBsAg, anti-HBc, anti-HDV, chronic active hepatitis B, and delta virus/ITP	Palmar erythema
4	HMC	A	73.2	28	M	175	0.6	11.4	3.9	Hemophilia A	None
5	HMC	A	86.3	50	M	168	1.2	11.9	4.7	HBsAg, hemophilia A	None
6	UNC	A	86.7	28	M	60	0.4	13.2	4.1	HBsAg	None
7	UNC	B	95	37	M	148	1.1	11.3	4.2	Anti-HBs, anti-HBc	None
8	UW	E	72.9	31	M	48 (107 − AST)	0.7	15.6	2.8	Hepatitis B, micronodular cirrhosis on biopsy	Hepatosplenomegaly, spider angioma

[a] Abbreviations: M, male, F, female; ALT, alanine aminotransferase; TB, total bilirubin; PT, prothrombin time; AST, aspartate aminotransferase; Alb, albumin; anti-HBs, hepatitis b virus surface antibody; anti-HBc, hepatitis b virus core antibody; HBsAg, hepatitis B virus surface antigen; anti-HDV, hepatitis delta virus antibody; HMC, Hershey Medical Center; UNC, University of North Carolina; UM, University of Massachusetts; UW, University of Washington.

[b] Group A, 1 × upper limit of normal (ULN) < ALT < 5 × ULN; group B, 5 × ULN ≤ ALT < 10 × ULN, TB, <1.5 mg/dl, PT, <2 s prolonged, no signs of clinical hepatic disease; group E, ALT ≥ 30 × ULN, or TB ≥5 mg/dl, or PT ≥5 s prolonged, or presence of clinical signs (e.g., ascites, varices, or other evidence of portal hypertension, or hepatic encephalopathy).

such as disseminated *Mycobacterium avium* complex or cytomegalovirus also may exhibit evidence of liver damage, and thus these patients may have altered ZDV pharmacokinetics, possibly leading to an increased risk of toxicity (2, 11).

AIDS Clinical Trial Group Protocol 062 was designed to examine the influence of hepatic disease on the pharmacokinetics and bioavailability of ZDV administered to asymptomatic HIV-infected patients. Results are compared with data obtained from HIV-seronegative cirrhotic patients, HIV-infected hemophiliacs with abnormal liver function tests, and HIV-infected patients and seronegative volunteers without evidence of liver disease (8, 13, 14, 22).

MATERIALS AND METHODS

Subjects. Eight volunteers with HIV infection and biochemical evidence of hepatic disease were enrolled in the study after written informed consent was obtained. This open-label study was approved by the Committee on the Protection of the Rights of Human Subjects for each institution. Participating centers included the University of North Carolina, University of Washington, University of Massachusetts, and Hershey Medical Center. Eligible patients were those with a Karnofsky performance scale of 60 or greater, 18 years of age or older, documentation of HIV infection by enzyme-linked immunosorbent assay with confirmation by Western blotting (immunoblotting), and laboratory or clinical evidence of hepatic disease. The subjects were stratified according to the results of commonly available liver function tests performed within 7 days of the study and the absence or presence of ascites (Table 1). Exclusion criteria included the presence of active opportunistic infections (with the exception of active or chronic hepatitis B virus or hepatitis delta virus infection) or ongoing therapy for an opportunistic infection, a platelet count of $<50{,}000/mm^3$, a polymorphonuclear leukocyte count of $<1{,}000/mm^3$, a creatinine concentration of >1.5 mg/dl, acute viral hepatitis within 30 days of study, cytotoxic chemotherapy or radiation therapy for Kaposi's sarcoma within 30 days of study, active drug or alcohol abuse, women taking birth control pills, pregnant women or women who are breast feeding, and patients on concomitant medications. Prior treatment with ZDV was not an exclusion if ZDV had been discontinued at least 48 h prior to study. Factor concentrate therapy was not an exclusion; all other medications were discontinued 48 h prior to the study. Each subject underwent a medical history review, physical examination, and laboratory evaluation within 1 week prior to commencement of the study. Liver function tests were repeated on the first day of the study. Follow-up evaluation 1 to 2 weeks after study doses were administered included a medical history, physical examination, and laboratory evaluation.

Drug administration. Two independent venous access sites were established—one for drug infusion and the other for blood sampling. Each subject received a single 120-mg i.v. dose of ZDV in 150 ml of 5% dextrose infused over 30 min on day 1. On day 2, a single 200-mg oral dose of ZDV (two 100-mg capsules) was administered with 200 ml of water. All subjects fasted for 8 h prior to each dose and for 2 h after each dose.

Sample collection. Blood samples (5 ml) were collected at the following times on days 1 and 2: 0 min (preinfusion or just prior to oral dose); 15 and 30 min (end of i.v. infusion); and 45, 60, 90, 120, 150, 180, 210, 240, 360, and 480 min after the beginning of the dose. The samples were centrifuged, and the serum was collected and frozen at −20°C.

Drug analysis. Before analysis, samples were heat inactivated at 56 to 58°C for 30 min. Concentrations of ZDV and GZDV in serum were determined by a high-performance liquid chromatography (HPLC) assay developed by Good et al. (10) with modifications (23, 26, 27). Briefly, both ZDV and GZDV were extracted on lipophilic type W columns with a DuPont Prep I automated sample processor (DuPont Co., Wilmington, Del.); each sample (0.5 ml) was placed on a column, washed with phosphate-buffered saline, and eluted with methanol. The methanol was evaporated, and the residue was reconstituted with 15% acetonitrile in water and injected into the HPLC. The column was a C_{18}-Resolve column (5 μm particle size; Waters Associates, Milford, Mass.). The mobile phase was 15% acetonitrile in 0.025 M potassium phosphate buffer (pH 2.20) at a flow rate of 1 ml/min. To reduce the chance of measuring an interfering substance coeluting with either ZDV or GZDV, the peaks eluting from the column were simultaneously measured at 266 and 254 nm. The ratio of peak heights at these wavelengths was compared with the corresponding ratios in the calibration sample and controls included in each assay batch. When the ratio in a patient's specimen differed by more than 10% (indicating a coeluting impurity), it was reassayed with a mobile phase with a higher pH (e.g., pH 2.5). The lower limits of detection were 0.04 μM ZDV and 0.05 μM GZDV. Interassay precision values (as percentage coefficients of variation) were 5% (3.6 μM), 5% (0.36 μM), and 19% (0.08 μM) for ZDV and 10% (2.1 μM), 13% (0.21 μM), and 14% (0.12 μM) for GZDV.

Pharmacokinetic analysis. Data were analyzed by noncompartmental methods with PCNONLIN version 4.2 model 200 for extravascular (oral) input and model 202 for i.v. infusion input. The terminal elimination rate constant (λz) was calculated from the slope of linear regression (least-squares method) of the logarithm of serum drug concentrations as a function of time in the terminal elimination phase. After visual inspection of the concentration-time profiles, 150 min (after i.v. administration) and 180 min (after oral administration) were selected as the first points for the calculation of λz. With only a few exceptions, five and six datum points were used to determine the terminal phase of elimination after oral and i.v. administration, respectively. The terminal $t_{1/2}$ was calculated as $0.693/\lambda z$. PCNONLIN uses the linear trapezoidal method to calculate area under the concentration (in serum)-time curve (AUC) from time zero to the time of the last sample (AUC_{last}) and is extrapolated to infinity. Other pharmacokinetic parameters were determined for ZDV and GZDV by standard noncompartmental methods (9, 19). The maximum concentration (C_{max}) and the time to achieve the maximum concentration (T_{max}) were obtained by visual inspection of each subject's serum drug concentration-time profile. The absolute bioavailability (F) was calculated by the equation (i.v. dose/oral dose) × (oral AUC/i.v. AUC). The AUC ratio of GZDV to ZDV was calculated with adjustment for the molecular weights of GZDV and ZDV (443 and 267, respectively). Data are reported as means ± standard deviations unless stated otherwise.

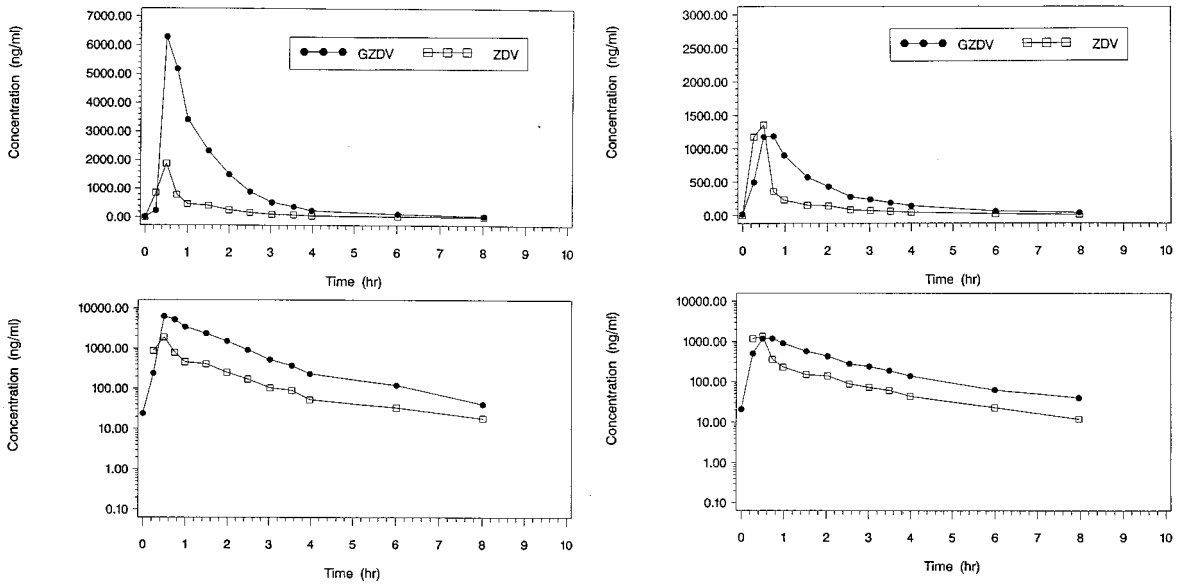

FIG. 1. Serum drug concentration-time profiles (patient 3) of ZDV and GZDV after oral (left) and i.v. (right) ZDV administration.

RESULTS

Liver disease category and demographic and laboratory data for each patient are shown in Table 1. Seven of eight subjects had mild hepatic disease (disease category A or B). One patient was classified as category E (severe liver disease) because of evidence of portal hypertension. If categorized according to Pugh's modification of Child's classification (15), seven of the eight subjects had mild dysfunction (Child-Pugh score, ≅5) and patient 8 had moderate dysfunction (Child-Pugh score, ≅7). The mean body weight of the eight subjects was 78.03 ± 11.50 kg (range, 59 to 95 kg). The mean age of the subjects was 34.5 ± 8.8 years. One female participated in this trial.

The drug concentration-time profiles (patient 3) for ZDV and GZDV obtained after oral and i.v. administration are shown in Fig. 1. The figure shows drug concentrations with linear (top panel) and logarithmic (bottom panel) coordinates. In all cases, the terminal portion of the GZDV serum drug concentration-time profile paralleled the decline of serum ZDV concentrations, indicating formation rate-limited elimination of the metabolite. Higher concentrations of GZDV were observed relative to ZDV concentrations after oral administration, consistent with hepatic first-pass extraction of ZDV.

Pharmacokinetic parameters after i.v. and oral ZDV administration are presented in Table 2. Table 3 shows the pharmacokinetic parameters for GZDV after ZDV administration.

TABLE 2. Pharmacokinetic parameters after ZDV administration[a]

Treatment	Patient	$AUC_{0-\infty}$ (ng · h/ml)	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)	MRT (h)	CL or CL/F (liters/h/kg)	V_{ss} (liters/kg)	F
ZDV (120 mg i.v.)	1	1,532	1,330	0.50	3.08	2.38	1.12	2.67	
	2	1,179	1,100	0.25	1.85	1.45	1.72	2.51	
	3	1,189	1,360	0.50	1.89	1.36	1.24	1.68	
	4	993	1,000	0.25	1.65	1.30	1.65	2.15	
	5	1,882	2,440	0.75	1.70	1.08	0.74	0.80	
	6	1,588	1,540	0.52	1.90	1.29	0.89	1.14	
	7	1,367	1,450	0.50	2.31	1.55	0.92	1.43	
Mean ± SD		1,386 ± 298	1,460 ± 472	0.50 (median)	2.05 ± 0.50	1.49 ± 0.42	1.18 ± 0.38	1.77 ± 0.70	
	8	1,284	1,230	0.50	1.95	1.67	1.28	2.13	
ZDV (200 mg oral)	1	1,539	1,590	0.25	2.44	1.72	1.87		0.60
	2	1,685	1,770	0.75	1.71	2.01	2.01		0.86
	3	1,776	1,890	0.50	2.04	1.74	1.38		0.90
	4	1,572	1,550	0.50	2.61	2.18	1.74		0.95
	5	2,018	1,760	0.75	1.55	2.10	1.15		0.64
	6	1,680	2,060	0.52	1.88	1.44	1.37		0.65
	7	1,421	1,640	0.52	2.04	1.96	1.48		0.62
Mean ± SD		1,670 ± 192	1,751 ± 180	0.52 (median)	2.04 ± 0.38	1.88 ± 0.26	1.57 ± 0.31		0.75 ± 0.15
	8	2,630	1,980	1.00	2.05	2.15	1.04		1.23

[a] Abbreviations: MRT, mean residence time; V_{ss}, volume of distribution at steady state.

TABLE 3. Pharmacokinetic parameters of GZDV after ZDV administration

Treatment	Patient	$AUC_{0-\infty}$ (ng · h/ml)	C_{max} (ng/ml)	T_{max} (h)	MRT (h)[a]	AUC_{GZDV}/AUC_{ZDV}
ZDV (120 mg i.v.)	1	3,205	1,350	0.79	2.18	1.26
	2	2,475	1,680	0.75	1.87	1.26
	3	2,356	1,190	0.73	2.11	1.19
	4	3,634	2,390	0.50	2.09	2.20
	5	3,341	1,620	0.75	2.13	1.07
	6	2,343	1,290	0.52	1.75	0.91
	7	1,925	1,330	0.50	1.46	0.84
Mean ± SD		2,754 ± 634	1,550 ± 411	0.73 (median)	1.94 ± 0.26	1.25 ± 0.45
	8	1,846	2,110	0.25	0.80	0.87
ZDV (200 mg oral)	1	7,537	3,310	0.78	2.18	3.00
	2	9,052	7,000	1.08	1.82	3.24
	3	7,687	6,290	0.50	1.64	2.61
	4	8,900	6,130	0.75	1.83	3.41
	5	8,106	4,190	1.00	2.49	2.42
	6	7,073	5,420	0.77	1.52	2.54
	7	5,440	4,200	0.77	1.65	2.31
Mean ± SD		7,685 ± 1,222	5,220 ± 1,350	0.77 (median)	1.88 ± 0.34	2.79 ± 0.43
	8	3,465	1,940	1.00	2.18	0.79

[a] MRT, mean residence time.

The apparent $t_{1/2}$s of GZDV were 1.71 ± 0.31 and 1.45 ± 0.12 h after i.v. and oral ZDV administration, respectively. Since GZDV appears to be formation rate limited, these values for the apparent $t_{1/2}$ of GZDV do not represent the true GZDV $t_{1/2}$.

DISCUSSION

The pharmacokinetics of ZDV and GZDV are altered in patients with hepatic disease. Table 4 shows comparative pharmacokinetic parameters of ZDV and GZDV in patients and volunteers with and without liver disease. All patients in the present study (AIDS Clinical Trials Group Protocol 062, Table 4), even those classified with mild hepatic impairment (seven of eight patients), had pharmacokinetic parameters that varied from those reported in healthy volunteers and HIV-infected patients without hepatic disease.

This discussion will focus on pharmacokinetic parameters after oral administration, since this is the most common route of ZDV administration, and there are extensive comparative data for this route of administration. After oral administration of ZDV to patients with liver disease in the present study, mean CL/F of ZDV (121.1 ± 13.4 liters/h) was less than that reported in HIV-infected men without liver disease (152.82 ± 61.38 liters/h) or in HIV-negative healthy subjects (153.72 ± 48.8 liters/h) (6, 21). Singlas and associates (21) concluded that the "pharmacokinetics of ZDV in healthy subjects is similar to that in HIV-seropositive patients with normal renal and hepatic function." Fletcher et al. compared the pharmacokinetics of ZDV in healthy volunteers ($n = 6$) with that in patients with AIDS ($n = 6$). After administration of a single 200-mg oral dose of ZDV, CL/Fs were 2.04 ± 0.46 and 1.78 ± 0.38 liters/h/kg for healthy volunteers and patients with AIDS, respectively (8). The ZDV CL/F in eight HIV-infected patients with hemophilia and mild hepatic impairment (Child-Pugh score, ≅5) given a single 300-mg oral dose was 1.68 ± 0.90 liters/h/kg, which is similar to the value reported in the present study (13). After 12 weeks of ZDV administration in five of the patients described above, the CL/F (1.63 ± 0.65 liters/h/kg) was relatively unchanged (14). The report by Morse et al. (14), as well as data from the present study, indicates that patients with mild liver disease cleared ZDV more slowly than HIV-positive or HIV-negative subjects without liver dysfunction.

The $t_{1/2}$s after oral dosing of ZDV in HIV-infected men and in healthy subjects were 1.04 ± 0.37 and 1.0 ± 0.20 h, respectively (6, 21). The ZDV $t_{1/2}$ in our study was prolonged (2.04 ± 0.38 h), which is consistent with the $t_{1/2}$ reported by Taburet et al. for HIV-negative patients with various degrees of liver cirrhosis (2.4 ± 1.2 h) and inconsistent with reports by Fletcher et al. and Morse et al. (8, 13, 22). Fletcher and colleagues reported a $t_{1/2}$ of 1.24 ± 0.20 h in patients with AIDS and unclassified moderate-to-severe hepatic disease ($n = 3$). The sampling scheme used by Fletcher et al., with the last collection time at 6 h, may have led to an underestimation of $t_{1/2}$ in this population. In the hemophiliac patients with mild hepatic impairment studied by Morse et al., the mean $t_{1/2}$s were 1.3 ± 0.5 h ($n = 3$) in patients showing biexponential elimination and 4.8 ± 2.8 h ($n = 5$) in patients showing triexponential elimination. However, the longer $t_{1/2}$ was calculated from only two datum points from three patients (13). Although the reported values appear to vary greatly, our results support a slightly prolonged $t_{1/2}$ in patients with hepatic dysfunction.

After an oral dose of 200 mg as capsules, peak concentrations were elevated in the present study (1,751 ± 180 ng/ml), compared with results reported by Taburet et al. in normal volunteers (1,067 ± 293 ng/ml), and less than the mean peak concentration in patients with biopsy-proven cirrhosis (2,880 ± 1,467 ng/ml) (22). F was slightly increased (75% ± 15%) in our patients with mild hepatic disease compared with historical values of approximately 64% (1).

In the present study, of seven patients with mild hepatic dysfunction given oral ZDV, the C_{max} and AUC of GZDV and the AUC ratio of GZDV to ZDV were reduced by approximately 21, 26, and 40%, respectively, compared with those of HIV-seronegative healthy volunteers (21). Clearly, less GZDV

TABLE 4. Comparative ZDV and GZDV pharmacokinetic parameters after oral administration[a]

Group	ZDV						GZDV				
	C_{max} (ng/ml)	T_{max} (h)	AUC (ng · h/ml)	$t_{1/2}$ (h)	CL/F (liters/h/kg)	F	C_{max} (ng/ml)	T_{max} (h)	AUC (ng · h/ml)	AUC_{GZDV}/AUC_{ZDV}	Apparent $t_{1/2}$ (h)
Asymptomatic HIV											
Mild hepatic disease, 200-mg capsule (ACTG 062, $n = 7$)[b]	1,751 ± 180	0.52[c]	1,670 ± 192	2.04 ± 0.38	1.57 ± 0.31	0.75 ± 0.15	5,220 ± 1,350	0.77[c]	7,685 ± 1,222	2.8 ± 0.4	1.5 ± 0.1
Hemophilia, 300-mg capsule ($n = 8$ [13])	2,052 ± 970[d]	0.5[e]	3,201 ± 1,694[d]	1.3 ± 0.5, 4.8 ± 2.8	1.68 ± 0.9		4,751 ± 2,269[d]	1–2[f]	8,097 ± 3,850[d]	1.5[g]	1.2 ± 0.5, 5.2 ± 3.7
HIV seronegative											
Cirrhosis, 200-mg capsule ($n = 14$ [22])	2,880 ± 1,467	0.8 ± 0.9	5,333 ± 1,573	2.4 ± 1.2	0.61 ± 0.22		3,230 ± 1,549	1.3 ± 0.9	11,062 ± 4,912	1.3 ± 0.6	2.4 ± 1.4
Normal volunteers 200-mg capsule ($n = 6$ [22])	1,067 ± 293	0.6 ± 0.2	1,387 ± 373	1.0 ± 0.4	2.28 ± 0.9		6,593 ± 1,549	0.8 ± 0.2	10,443 ± 2,080	4.6 ± 0.7	0.9 ± 0.2
AIDS or AIDS-related complex, 250-mg capsule ($n = 5$ [1])	1,180 ± 590[h]	0.85 ± 0.4	1,800 ± 650[h]	0.9 ± 0.3,[i] 1.2 ± 0.3[i]	1.87[g]	0.64 ± 0.10					

[a] Values with ± are means ± standard deviations.
[b] Seven of eight patients had mild hepatic disease. ACTG 062, AIDS Clinical Trials Group Protocol 062.
[c] Median value.
[d] Data not dose normalized.
[e] Mean mentioned in text.
[f] Range mentioned in text.
[g] Calculated from mean data.
[h] Dose normalized to a 200-mg capsule.
[i] Results from solution (6.0 and 15.0 mg/kg/day).

metabolite is formed in patients with hepatic impairment. Although only one patient (patient 8) had moderate hepatic dysfunction with evidence of portal hypertension, it is interesting to note he had the lowest AUC ratio of GZDV to ZDV (0.79). Likewise, the GZDV AUC (3,465 ng · h/ml) in this patient was relatively small. The mean apparent $t_{1/2}$ (1.45 ± 0.12 h) of GZDV was increased in the patients studied compared with that of healthy subjects (22). The elimination of GZDV is rate limited by its formation, as evidenced by its parallel decay with ZDV. Again, these results are consistent with previous data suggesting impaired ZDV elimination in hepatic disease (8, 13, 22).

The results of the present study show that the hepatic metabolism of ZDV is impaired in patients with mild hepatic dysfunction. The glucuronidation of ZDV is catalyzed by UDP-glucuronosyltransferase (UDPGT) (17). At least five different human UDPGT isozymes are known, and several forms have yet to be adequately characterized (25). Existing data suggest that UDPGT2 is involved primarily in ZDV glucuronidation in humans (16). Endogenous compounds that accumulate in cirrhosis and hepatitis and are substrates for this isozyme of UDPGT may interfere with ZDV glucuronidation (24).

Drug disposition can be altered in hepatic disease because of changes in hepatic blood flow, enzyme activity (amount of available enzymes), plasma protein binding, or the development of portosystemic shunts. The pharmacokinetic differences observed in asymptomatic HIV-infected patients with liver dysfunction may have an impact on ZDV dosing during extended therapy. Seven of the patients studied in this report had only mild hepatic impairment, and yet differences in exposure (on the basis of the AUC and C_{max}) and elimination were observed. In general, increased C_{max}, increased AUC, decreased CL/F, and a slightly prolonged $t_{1/2}$ were observed in this population. These results suggest that a dose reduction or extended dosing intervals may be necessary in patients with liver dysfunction to diminish the risk of ZDV toxicity which has been associated with elevated concentrations of ZDV in serum.

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